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| 09/600,564 | 11/07/2000 | Florian Kern | KREISLER1089 | 5234 |

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| EXAMINER |
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ZEMAN, ROBERT A

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| ART UNIT | PAPER NUMBER |
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1645

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|--|------------|---------------|
| 3 MONTHS | 03/02/2007 | PAPER |

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

09/600,564

Applicant(s)

KERN ET AL.

Examiner

Robert A. Zeman

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 11 December 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 14-27 is/are pending in the application.
- 4a) Of the above claim(s) 22-26 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 14-21 and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-11-2006 has been entered.

The amendment and response filed on 12-11-2006 are acknowledged. Claims 14 and 27 have been amended. Claims 14-27 are pending. Claims 22-26 remain withdrawn from consideration as being drawn to non-elected invention(s). Claims 14-21 and 27 are currently under examination.

Declaration

The Declaration by Dr. Dirk Busch filed on 12-11-2006 is acknowledged and has been fully considered.

The Declaration by Dr. Michael Raymond Betts filed on 12-11-2006 is acknowledged and has been fully considered.

Claim Rejections Withdrawn

The rejection of Claims 14-21 and 27 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in light of the amendment to claims 14 and 27.

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The new matter rejection of claims 14-21 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement based on the limitation “proliferation accompanied by the elimination of T cells do not occur.” is withdrawn in light of the amendment thereto.

The rejection of claims 27 under 35 U.S.C. 112, second paragraph, as being rendered vague and indefinite by the phrase “selection and proliferation accompanied by the specific elimination of particular T cells do not occur” is withdrawn in light of the amendment thereto.

Claim Rejections Maintained

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The new matter rejection of claim 16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement based on the limitation “the suspension comprises **cells which present the protein fragment bound to MHC class I or class II molecules.**” is maintained for reasons of record.

Contrary to Applicant’s assertion support for said limitation does not appear in the specification at page 7, second paragraph nor does this phrase does not appear in the specification, or original claims as filed. The cited portion of the specification recites “said suspensions containing T cells contain cells which present the protein fragment essentially with

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MHC I or II molecules...". Said phrase does not provide support, either explicit or implicit, for the limitation recited in claim 16. Therefore this limitation is new matter.

New Claim Objections

Claim 27 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 14.

When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

New Grounds of Rejection

35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-21 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 is rendered vague and indefinite by the use of the phrase "cleaving the amino acid sequence of said antigen" in step c). It is unclear how a sequence can be cleaved as they constitute an abstraction.

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Claim 14 is rendered vague and indefinite by the use of the phrase "at least one activation marker expressed or expression enhanced due to the T cell stimulation by the protein fragment or fragments which has been induced or expression enhanced by the protein fragment or fragments...". It is unclear how said fragments can be "induced or expression enhanced" by itself. Moreover, it is unclear what is meant by the term "expression-enhanced". Consequently, it is impossible to determine the metes and bounds of the claimed invention.

Claim 14 and 27 are rendered vague and indefinite by the use of the phrase "...taken up by the major to his compatibility antigen (MHC) molecules...". It is unclear what is meant by said phrase.

Claim 14 is rendered vague and indefinite by the use of the phrase "selection and proliferation". It is unclear what cell population said phrase is drawn to.

Claim 16 recites the limitation "the suspension"" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 14-19, 21 and 27 are rejected under 35 U.S.C. 102(a) as being anticipated by Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237).

The instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- providing (synthesizing) at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

The aforementioned method also requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration “sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible” and “... sufficiently short so that selection and proliferation accompanied by the specific elimination of stimulated T cells do not occur”.

Yanagisawa et al. disclose methods of mapping T cell epitopes on mycobacterial antigens by measuring the usage of the TCR β chair repertoire by flow cytometry. Yanagisawa et al. further disclose the addition of 15-mer peptides, overlapping by five amino acids, covering the complete MPT59 protein to T cell suspensions prepared from the inguinal lymph nodes from various strains of mice (see page 228). The expression of cell surface antigens (including TCR V_{β}) was measure before and after culturing (see page 229).

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With regard to the limitation that the incubation time be sufficiently short so that selection, proliferation and the specific elimination of stimulated T cells does not occur, it is deemed, in absence to evidence to the contrary, that since the active expression of cell surface markers are measured on the stimulated T cells, said cells could not have been specifically eliminated.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 14-21 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanagisawa et al. (International Immunology, 1997, Vol. 9 No. 2, pages 227-237) and Picker et al. (Blood, 1995, Vol. 86 No. 4, pages 1408-1419 -- IDS).

The instant claims are drawn to methods for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- providing (synthesizing) at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

The aforementioned method also requires that the incubation time of the protein fragment(s) with cell suspension containing T cells be of a duration “sufficiently long so that the protein fragment or fragments are sufficiently taken up by the major histocompatibility antigen (MHC) molecules said taking up being sufficient when an unambiguous identification of stimulated T cells is possible” and “... sufficiently short so that selection and proliferation accompanied by the specific elimination of stimulated T cells do not occur”.

Yanagisawa et al. disclose methods of mapping T cell epitopes on mycobacterial antigens by measuring the usage of the TCR β chain repertoire by flow cytometry. Yanagisawa et al. further disclose the addition of 15-mer peptides, overlapping by five amino acids, covering the complete MPT59 protein to T cell suspensions prepared from the inguinal lymph nodes from various strains of mice (see page 228). The expression of cell surface antigens (including TCR

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V_{β} was measure before and after culturing. Additionally the production of IFN- γ , IL-10, IL-5 and IL-4 was measured (see page 229).

Yanagisawa et al. differs from the instant invention in that the cytokine levels are measured by ELISA.

Picker et al. disclose a multiparameter flow cytometric assay that allows the simultaneous determination of an individual T cell's ability to produce multiple cytokines and its phenotypes after a short (4 to 8) *in vitro* incubation with an activating stimulus (antigen) [see abstract].

Picker et al. further disclose that said T cells could be contained in peripheral blood samples (see page 1409).

It would have been obvious for one of ordinary skill in the art at the time of the invention to use the flow cytometry method of Picker et al. in the epitope mapping method of Yanagisawa et al. in order to take advantage rapid ability to determine the functional potential (i.e. response) of phenotypically distinct T cell subsets.

One would have had a reasonable expectation of success since Picker et al. disclose that the "simplicity and rapidity" of their detection technique coupled with the widespread availability of flow cytometers and T cell phenotyping antibodies suggest that their technique could be broadly applicable to the evaluation of immune status (see page 1418).

Conclusion

No claim is allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



ROBERT A. ZEMAN
PRIMARY EXAMINER

February 28, 2007